US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rul s 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PF-0634 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/27009	12/11/1999	12/11/1998

Applicant

INCYTE PHARMACEUTICALS, INC ET AL

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readble form.

   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   ☐ as suggested by the applicant.

   ☐ because the applicant failed to suggest a figure.

   ☐ because this figure better characterizes the invention.

   ☒ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As invention 1, but relating to SEQ ID Nos:10 and 26.

11. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:11 and 27.

12. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:12 and 28.

13. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:13 and 29.

14. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:14 and 30.

15. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:15 and 31.

16. Claims: 1-20, all partially

As invention 1, but relating to SEQ ID Nos:16 and 32.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17, 18

Claims 17 and 18 were not searched because the claimed compounds were not sufficiently characterised.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

International Application No
PCT/US 99/27009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/55 C12N9/14 C12Q1/68 C12N1/21 A61K38/46
C07K16/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] AC Z98304, 11 August 1997 (1997-08-11) GRAFHAM D: "Human DNA sequence from clone 54B20 on chromosome Xp11.1-11.3" XP002133630 99.6% identity in 234 nt overlap with SEQ ID No:17 (313-80:109182-109415) ---	3-6,9
X	DATABASE EMBL [Online] AC X60237, 2 December 1991 (1991-12-02) SWANSON KW ET AL: "C. aethiops mRNA for lysozyme" XP002133631 59.3% identity in 428 nt overlap ---	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2000	05.07.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lejeune, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 00553 A (INCYTE PHARMA INC ;AU YOUNG JANICE (US); HAWKINS PHILLIP R (US); H) 8 January 1998 (1998-01-08) abstract	

A	EP 0 811 687 A (HAYASHIBARA BIOCHEM LAB) 10 December 1997 (1997-12-10) abstract	

Information on patent family members

International Application No
PCT/US 99/27009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800553 A	08-01-1998	US 5958750 A	28-09-1999
		AU 3409897 A	21-01-1998
		US 5854046 A	29-12-1998
		US 6057110 A	02-05-2000
EP 0811687 A	10-12-1997	JP 10057080 A	03-03-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

PASQUALONE, Danielle
Legal Department
Incyte Pharmaceuticals, Inc.
3174 Porter Drive
Palo Alto, CA 94304
ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 08 November 2001 (08.11.01)	
Applicant's or agent's file reference PF-0634 PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/27009	International filing date (day/month/year) 12 November 1999 (12.11.99)
International publication date (day/month/year) 18 May 2000 (18.05.00)	Priority date (day/month/year) 12 November 1998 (12.11.98)
Applicant INCYTE PHARMACEUTICALS, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk**(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
12 Nove 1998 (12.11.98)	60/172,256	US	22 Octo 2001 (22.10.01)
21 May 1999 (21.05.99)	60/135,519	US	15 Febr 2000 (15.02.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Magda BOUACHA

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 November 2000 (09.11.00)	
International application No. PCT/US99/27009	**Applicant's or agent's file reference** PF-0634 PCT
International filing date (day/month/year) 12 November 1999 (12.11.99)	**Priority date** (day/month/year) 12 November 1998 (12.11.98)
Applicant TANG, Tom, Y. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 June 2000 (06.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nestor Santesso
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/55, 9/14, C12Q 1/68, C12N 1/21, A61K 38/46, C07K 16/40

A2

(11) International Publication Number: WO 00/28045

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/US99/27009

(22) International Filing Date: 12 November 1999 (12.11.99)

(30) Priority Data:

60/172,256	12 November 1998 (12.11.98)	US
60/135,519	21 May 1999 (21.05.99)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	60/172,256 (CIP)
Filed on	12 November 1998 (12.11.98)
US	60/135,519 (CIP)
Filed on	21 May 1999 (21.05.99)

(71) Applicant *(for all designated States except US)*: INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TANG, Tom, Y. [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive, #12, Mountain View, CA 94040 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). BANDMAN, Olga [US/US]; 366 Anna Avenue, Mountain View, CA 94043 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue, #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). LU, Dyung, Aina, M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). YANG, Junming [CN/US]; 7136 Clarendon Street, San Jose, CA 95129 (US).

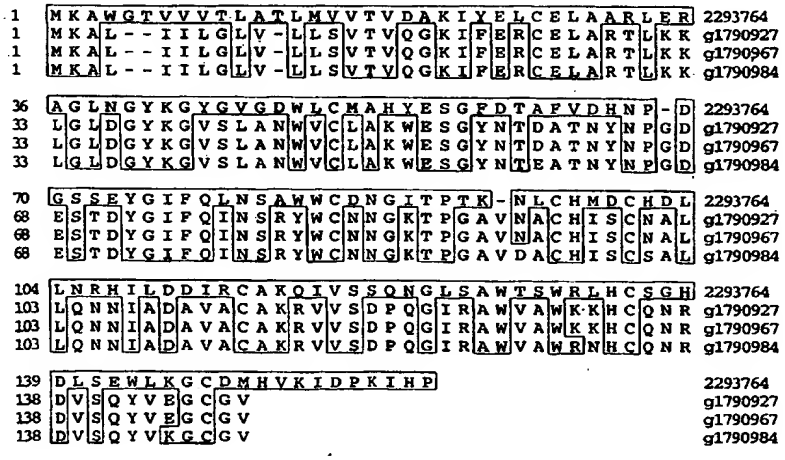
(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: HUMAN HYDROLASE PROTEINS



(57) Abstract

The invention provides human hydrolase proteins (HYDRL) and polynucleotides which identify and encode HYDRL. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of HYDRL.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
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DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
LUCY J. BILLINGS
INCYTE PHARMACEUTICALS, INC.
3174 PORTER DRIVE
PALO ALTO, CA 94304

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	
Applicant's or agent's file reference PF-0634 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US99/27009	12 November 1999 (12.11.1999)	12 November 1998 (12.11.1998)

Applicant

INCYTE PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	David J. Steadman
Facsimile No. (703)305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PF-0634 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/27009	International filing date *(day/month/year)* 12 November 1999 (12.11.1999)	Priority date *(day/month/year)* 12 November 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/55, 9/14; C12Q 1/68, 1/21; A61K 38/46; C07K 16/40 and US Cl.: 435/195, 6, 320.1, 325, 410, 243, 71.1; 514/2; 530/387.9; 536/23.2		
Applicant INCYTE PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 June 2000 (06.06.2000)	07 August 2002 (07.08.2002)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer David J. Steadman Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/27009

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-71 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 72 and 73, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-30, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/27009

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 17, 18, and 1-16, 20 (in part)

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 17, 18 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 17, 18 were not examined because the claimed agonist and antagonist or method of use thereof have not been sufficiently characterized.

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 17 and 18 and 1-16, 19-20 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	15, 16, 19, 20 (in part)	YES
	Claims	1-14 (in part)	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-16, 19, 20 (in part)	NO
Industrial Applicability (IA)	Claims	1-16, 19, 20 (in part)	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

1. Claims 1-14 lack novelty under PCT Article 33(2) as being anticipated by Swanson et al. Swanson et al. teach the polynucleotide sequence of a mRNA isolated from *Cercopithecus aethiops* encoding a polypeptide with lysozyme activity. Swanson et al. further teach the polypeptide sequence encoded by the *C. aethiops* mRNA. The polynucleotide of Swanson et al. shares 59.3 % sequence homology with a 428 nt overlap of SEQ ID NO:17. Furthermore, the polypeptide of Swanson et al. comprises at least a single amino acid fragment that is identical to SEQ ID NO:1.

2. Claims 15, 16, 19, and 20 lack an inventive step under PCT Article 33(3) because it would have been obvious to produce an antibody that binds the polypeptide of Swanson et al., prepare a pharmaceutical composition comprising the polypeptide of Swanson et al., or prepare an antagonist of the polypeptide of Swanson et al.

3. Claims 1-16, 19, and 20 meet the criteria set out in PCT Article 33(4) because the polynucleotides as encompassed by the claims are useful for protein expression, the polypeptides as encompassed by the claims are useful for antibody production, and the antibodies as encompassed by the claims are useful for protein purification.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Please See Continuation Sheet

Supplemental Box
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VIII. The following observations on the clarity of the claims, description, and drawings or on the questions are made:

1. Claims 1-16, 19, and 20 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

Claims 1 (claims 2-8, 12-16, 19, and 20 dependent thereon) and 9 (claims 10 and 11 dependent thereon) are directed to polypeptide and polynucleotide fragments corresponding to portions of SEQ ID NO:1 and SEQ ID NO:17, respectively. Claims 1-16 are objected to because the claims are directed to a genus of polypeptides derived from SEQ ID NO:1 and polynucleotides derived from SEQ ID NO:17 including fragments of SEQ ID NOs:1 and 17 that have not been disclosed in the description. No description has been provided of the fragments of the polypeptide and polynucleotide sequences encompassed by the claims. No information, beyond the characterization of SEQ ID NOs:1 and 17 has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptide or polynucleotide fragments. Also, the description does not describe the function of all the polypeptide sequences derived from SEQ ID NO:1 or polypeptides encoded by the polynucleotide sequences derived from SEQ ID NO:17, including fragments and variants within the scope of the claimed genus. The genus of polypeptides and polynucleotides claimed is a large variable genus. Therefore, many functionally unrelated polypeptides are encompassed within the scope of these claims. There is disclosed only a single species of the claimed genus of polypeptides or polynucleotides, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

2. Claims 1-16, 19, and 20 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Claims 1 (claims 2-8, 12-16, 19, and 20 dependent thereon) and 9 (claims 10 and 11 dependent thereon) are so broad as to encompass any fragment of SEQ ID NO:1, polynucleotide encoding thereof, or any fragment of SEQ ID NO:17. The scope of the claims is not commensurate with the enablement provided by the description with regard to the extremely large number of polypeptide and polynucleotide fragments broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and

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functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the description is limited to the polypeptide of SEQ ID NO:1, a polynucleotide encoding thereof, and the polynucleotide of SEQ ID NO:17.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The description does not support the broad scope of the claims which encompass all modifications and fragments of the polypeptide of SEQ ID NO:1, polynucleotides encoding thereof, or the polynucleotide of SEQ ID NO:17 because the description does not establish: (A) regions of the protein structure which may be modified without affecting activity; (B) the general tolerance of the claimed polypeptides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying residues of the claimed polypeptides with an expectation of obtaining the desired biological function; and (D) the description provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino or nucleic acid modifications of any fragment of the polypeptide of SEQ ID NO:1 or polynucleotides encoding thereof or the polynucleotide of SEQ ID NO:17. Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

3. Claim 5 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claim is indefinite for the following reason(s): claim 5 is indefinite in the recitation of "stringent conditions" as the description does not define what conditions constitute "stringent". What hybridization conditions are considered "stringent" varies widely in the art depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a polynucleotide encoding SEQ ID NO:1 a sequence must be to be included within the scope of these claims.